

## PATENT COOPERATION TREATY

PCT

## NOTIFICATION OF ELECTION

(PCT Rule 61.2)

From the INTERNATIONAL BUREAU

To:

United States Patent and Trademark  
Office  
(Box PCT)  
Crystal Plaza 2  
Washington, DC 20231  
ÉTATS-UNIS D'AMÉRIQUE

in its capacity as elected Office

<b>Date of mailing (day/month/year)</b> 08 January 1999 (08.01.99)	<b>Applicant's or agent's file reference</b> PCT 0685
<b>International application No.</b> PCT/NL98/00213	<b>Priority date (day/month/year)</b> 15 April 1997 (15.04.97)
<b>International filing date (day/month/year)</b> 15 April 1998 (15.04.98)	
<b>Applicant</b> NOTEBORN, Matheus, Hubertus, Maria et al	

1. The designated Office is hereby notified of its election made:

☒ in the demand filed with the International Preliminary Examining Authority on:

16 November 1998 (16.11.98)

☐ in a notice effecting later election filed with the International Bureau on:2. The election ☒ was☐ was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

<b>The International Bureau of WIPO</b> 34, chemin des Colombettes 1211 Geneva 20, Switzerland	<b>Authorized officer</b> N. Fischer
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

09/403213

## INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference <b>PCT 0685</b>	<b>FOR FURTHER ACTION</b> see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
International application No. <b>PCT/NL 98/00213</b>	International filing date (day/month/year) <b>15/04/1998</b>	(Earliest) Priority Date (day/month/year) <b>15/04/1997</b>
Applicant <b>LEADD B.V. et al.</b>		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 5 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

1. ☒ **Certain claims were found unsearchable** (see Box I).
2. ☐ **Unity of invention is lacking** (see Box II).
3. ☐ The international application contains disclosure of a **nucleotide and/or amino acid sequence listing** and the international search was carried out on the basis of the sequence listing
  - ☐ filed with the international application.
  - ☐ furnished by the applicant separately from the international application.
    - ☐ but not accompanied by a statement to the effect that it did not include matter going beyond the disclosure in the international application as filed.
  - ☐ Transcribed by this Authority
4. With regard to the **title**,
  - ☒ the text is approved as submitted by the applicant
  - ☐ the text has been established by this Authority to read as follows:
5. With regard to the **abstract**,
  - ☒ the text is approved as submitted by the applicant
  - ☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this International Search Report, submit comments to this Authority.
6. The figure of the **drawings** to be published with the abstract is:  
Figure No. \_\_\_\_\_
  - ☐ as suggested by the applicant.
  - ☐ because the applicant failed to suggest a figure.
  - ☐ because this figure better characterizes the invention.

☒ None of the figures.

# INTERNATIONAL SEARCH REPORT

International application No.

PCT/NL 98/00213

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:  
Please see Further Information sheet enclosed.
2. ☐ Claims Nos.:  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Remark: Although claims 17-19, in as far as they concern an in vivo method, are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

# INTERI ONAL SEARCH REPORT

International Application No  
PCT/NL 98/00213

<b>A. CLASSIFICATION OF SUBJECT MATTER</b> IPC 6 C12N15/34 C07K14/01 C12N15/86 C12N5/10 A61K48/00 C12Q1/68		
According to International Patent Classification (IPC) or to both national classification and IPC		
<b>B. FIELDS SEARCHED</b> Minimum documentation searched (classification system followed by classification symbols) IPC 6 C07K C12N		
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched		
Electronic data base consulted during the international search (name of data base and, where practical, search terms used)		
<b>C. DOCUMENTS CONSIDERED TO BE RELEVANT</b>		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 95 03414 A (AESCULAAP BV ;NOTEBORN MATHEUS HUBERTUS MARI (NL); KOCH GUUS (NL)) 2 February 1995	1-8, 12-21
Y	see page 8, line 30 - page 10, line 24 see page 16, line 1 - page 21, line 7 see page 28, line 6 - page 30, line 9; claims 1-33	9-11
Y	WO 96 30512 A (RHONE POULENC RORER SA ;BRACCO LAURENT (FR); SCHWEIGHOFFER FABIEN) 3 October 1996 see claims 15,49-52	9-11
-/--		
<input checked="" type="checkbox"/> Further documents are listed in the continuation of box C. <input checked="" type="checkbox"/> Patent family members are listed in annex.		
* Special categories of cited documents : <div style="display: flex; justify-content: space-between;"> <div style="width: 45%;"> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> </div> <div style="width: 45%;"> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</p> <p>"&amp;" document member of the same patent family</p> </div> </div>		
Date of the actual completion of the international search  <div style="text-align: center; font-size: 1.2em;">1 July 1998</div>		Date of mailing of the international search report  <div style="text-align: center; font-size: 1.2em;">28.07.98</div>
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016		Authorized officer  <div style="text-align: center; font-size: 1.2em;">Gurdjian, D</div>

## INTERNATIONAL SEARCH REPORT

International Application No

PCT/NL 98/00213

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	ZHUANG, SHI-MEI ET AL: "Differential sensitivity to Ad5 E1B-21kD and Bcl-2 proteins of apoptin -induced versus p53-induced apoptosis" CARCINOGENESIS (1995), 16(12), 2939-44 CODEN: CRNGDP;ISSN: 0143-3334, XP002038753 see the whole document ---	1,3-19
P,X	PIETERSEN A M ET AL: "Adenoviral vectors expressing apoptin: Tools for tumor-specific gene therapy" CANCER GENE THERAPY, 4 (6 CONF. SUPPL.). 1997. S16-S17., XP002069965 see the whole document -----	1-21

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/NL 98/00213

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
W0 9503414 A	02-02-1995	NL 9301272 A	16-02-1995
		AU 7547394 A	20-02-1995
		CA 2167578 A	02-02-1995
		EP 0784685 A	23-07-1997
		JP 9504941 T	20-05-1997
		ZA 9405275 A	24-02-1995
W0 9630512 A	03-10-1996	FR 2732348 A	04-10-1996
		AU 5402096 A	16-10-1996
		CA 2214451 A	03-10-1996
		CZ 9703080 A	14-01-1998
		EP 0817845 A	14-01-1998
		NO 974449 A	26-09-1997

## PATENT COOPERATION TREATY

## PCT

REC'D 20 JUL 1999

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## INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference PCT 0685	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416) <b>FOR FURTHER ACTION</b>	
International application No. PCT/NL98/00213	International filing date (day/month/year) 15/04/1998	Priority date (day/month/year) 15/04/1997
International Patent Classification (IPC) or national classification and IPC C12N15/34		
Applicant LEADD B.V. et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.



2. This REPORT consists of a total of 7 sheets, including this cover sheet.

- ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☒ Priority
- III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☒ Certain defects in the international application
- VIII ☒ Certain observations on the international application

Date of submission of the demand  16/11/1998	Date of completion of this report  16.07.99
Name and mailing address of the international preliminary examining authority:  European Patent Office D-80298 Munich Tel. (+49-89) 2399-0 Tx: 523656 epmu d Fax: (+49-89) 2399-4465	Authorized officer  Hermann, K  Telephone No. (+49-89) 2399 2670 



# INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/NL98/00213

## I. Basis of the report

1. This report has been drawn on the basis of *(substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.)*:

### Description, pages:

1-36 as originally filed

### Claims, No.:

1-21 as originally filed

### Drawings, sheets:

1/7-7/7 as originally filed

2. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

## II. Priority

1. ☐ This report has been established as if no priority had been claimed due to the failure to furnish within the prescribed time limit the requested:
- ☐ copy of the earlier application whose priority has been claimed.
  - ☐ translation of the earlier application whose priority has been claimed.
2. ☐ This report has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid.

# INTERNATIONAL PRELIMINARY EXAMINATION REPORT

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Thus for the purposes of this report, the international filing date indicated above is considered to be the relevant date.

## 3. Additional observations, if necessary:

**see separate sheet**

## V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

### 1. Statement

Novelty (N)	Yes:	Claims	2, 3, 5, 7, 9, 10, 15, 16, 18, 19
	No:	Claims	1, 4, 6, 8, 11-14, 17, 20, 21
Inventive step (IS)	Yes:	Claims	3
	No:	Claims	1, 2, 4- 21
Industrial applicability (IA)	Yes:	Claims	1-16, 21 (claims 17-20: see item V, point 4.2)
	No:	Claims	

### 2. Citations and explanations

**see separate sheet**

## VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

**see separate sheet**

## VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

**see separate sheet**

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT - SEPARATE SHEET**

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**Citations**

The documents mentioned in this international preliminary examination report (IPER) are numbered as in the international search report dated 01.07.98, i.e. D1 corresponds to the first document of the search report etc. Reference is made to the following documents:

**D1:** WO-A-9503414

**D2:** WO-A-9630512

**Re ITEM II (Priority)**

Since the priority documents pertaining to the present application are not yet available to the IPEA, this IPER has been drawn up considering the priority dates (15.04.97 and 18.11.97) as valid. **D4** (Pietersen, A.M. et al.) has been published between the priority date and the filing date of the present application. Thus, said document does not constitute prior art in the meaning of Rule 64(1)(b) PCT. However, if it turns out that the effective date of the claimed subject-matter is not the priority date then **D4** will become relevant to assess whether the present application satisfies the criteria set forth in Art. 33(2) and (3) PCT.

**Re ITEM V (Novelty, inventive step, industrial applicability)**

**1 Summary of the present application**

The present application is related to anti-tumor therapies. Tumor cells are infected by gene delivery vehicles containing the coding sequence for a protein with apoptin-like activity. The application is also related to host cells comprising said gene delivery vehicle. Furthermore, the application is related to the use of said gene delivery vehicles in cancer treatment and diagnosis.

**2 Novelty (Art. 33(2) PCT)**

- 2.1 The subject-matter of claims 2, 3, 5, 7, 9, 10, 15, 16, 18 and 19 has not been made available to the public by any of the available prior art documents and can

therefore be regarded as novel.

2.2 The subject-matter of claims 1, 4, 6, 8, 11-14, 17, 20 and 21 does not meet the requirements of Art. 33(2) and 33(3) PCT.

2.3 **D1** discloses cells infected with a viral vector comprising a nucleic acid molecule encoding for CAV protein VP1, VP2 or VP3 alone, a combination VP1, VP2 or VP3 or all three simultaneously (D1, p. 5, l. 10-15). Retroviral vectors that contain a coding sequence for VP3 are also disclosed in **D1** (p. 8, l. 24-25). **D1** therefore deprives claims 1, 4, 6, 8, 11 and 14 of novelty.

2.4 **D1** also discloses the coupling of CAV proteins VP2 and/or VP3 to a ligand (e.g. an antibody) having affinity to a tumor-associated antiligand (D1, p. 8, last par.). Therefore, claims 12 and 13 do not meet the requirements of Art. 33(2) and (3) PCT.

2.5 **D1** further discloses the use of a gene delivery vehicle comprising a nucleic acid molecule encoding for CAV protein VP3 for inducing apoptosis in tumor cells (D1, p. 28, l. 6). VP3 expression and induction of apoptosis was analyzed in vitro by staining the transfected cells (D1, p. 29, l. 2-5). Thus, **D1** also destroys the novelty of claims 17, 20 and 21.

### **3 Inventive step (Art. 33(3) PCT)**

3.1 The subject-matter of claim 3 cannot be derived from the available prior art in an obvious manner and therefore complies with the requirements of Art. 33(3) PCT.

3.2 The closest prior art concerning claims 9, 10, 15 and 16-21 is **D1**. **D1** discloses cells infected with a retroviral vector comprising a nucleic acid molecule encoding for CAV protein VP3 (D1, p. 8, l. 24-25).

3.3 **D1** differs from the present application in that the use of adenoviruses and replication-deficient viruses is not mentioned. The underlying problem can therefore be seen in the provision of alternative methods for the gene therapy of tumor cells. In the art of gene therapy the use of numerous viruses is well-

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT - SEPARATE SHEET**

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established. In **D2**, for instance, adenoviruses are used (see **D2**, p. 17, l. 20-22 and claim 50). The Applicant himself states that replication-deficient viruses in combination with helper cells "such as cell line 293, the 911 cell line and the PER.C6 cell line" represent state of the art tools for gene therapy (p. 3, l. 36-p. 4, l. 18).

- 3.4 The IPEA is therefore of the opinion that a person skilled in the art, would be prompted to use the viruses and helper cells well-established in the art of gene therapy in analogous manner to **D1** and thus arrive at the subject-matter of claims 9, 10, 15 and 16-21 without the exercise of inventive skill.
- 3.5 Furthermore, the subject-matter of claims 2, 5 and 7 does not contribute to an inventive solution of an unexpected technical problem. The "modifications" of the translation initiation site are not required to show any unexpected effect (Art. 33(3) PCT.

**4 Industrial applicability (Art. 33(4) PCT)**

- 4.1 Claims 1-16, 21 meet the criteria as set forth by Art. 33(4) PCT.
- 4.2 For the subject-matter of claims 17-20 (in so far as *in vivo* methods on the human or animal body are concerned) no unified criteria exist among the PCT member states for the assessment whether it is industrially applicable or not. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but will allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

**Re ITEM VII (Certain defects in the international application)**

As pointed out under **ITEM VIII, 3**, infra, references given in the disclosure do not correspond to the list of references given on p. 32-36 or are not unambiguously identifiable.

**Re ITEM VIII (Clarity and support by the description)**

- 1 Rule 6.3(a) PCT requires that the matter for which protection is sought be defined in terms of technical features of the invention. A nucleic acid molecule (claims 1, 2 and 4-6) is a chemical compound which can be clearly and unambiguously defined by its chemical structure, i.e., its nucleic acid sequence. The characterization of a product only by the desired function without any real technical meaning does not seem to be allowable (Art. 6 PCT).
- 2 Features which are not disclosed in the description of the invention as originally filed but which are only described in a cross-referenced document can only be introduced into the claims without contravening Art. 34(2)(b) PCT if such features (i) at least implicitly clearly belong to the description as filed and (ii) are precisely defined and identifiable within the disclosure of the reference document.
- 3 However, the IPEA was not able to check whether the nucleotide or amino acid positions given in present application (p. 11, l. 2 and l. 4; p. 19, l. 33) are precisely defined within the reference documents. The cross-references made in present description are obscure since "Noteborn and De Boer, 1990" (p. 10, l. 35) cannot be found in the references given on p. 32-36, "Noteborn et al. 1994" (p. 11, l. 1) exists twice and one reference has not even been published (p. 11, l. 3). The IPEA is therefore of the opinion that the description does not disclose the invention in a manner sufficiently clear and complete for the invention to be carried out by a person skilled in the art (Art. 5 PCT).
- 4 The wording "apoptin-like activity" (claim 1) and "VP2-like activity" (claim 4) is ambiguous as far as said activities are not clearly and unambiguously disclosed in said claims. Furthermore, if said activity is intended to the induction of apoptosis, the claims embrace any nucleic acid molecule encoding a protein with such activity e.g. p53.
- 5 Regarding claim 18, the IPEA is of the opinion that the term in brackets ("chemo") renders the scope of said claim unclear (Art. 6 PCT).